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Effective Use of Tociluzimab, an Anti-Interleukin 6 Agent for the Treatment of Steroid-Refractory Grade IV Intestinal Acute Graft-Versus-Host Disease in a Child with Sickle Cell Disease

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Topic Significance & Study Purpose/Background/Rationale: The success of allogeneic hematopoietic cell transplantation (AlloHCT) continues to be limited by the incidence of acute graft-versus-host disease (aGVHD), a serious and sometimes fatal complication. Steroid-refractory aGVHD (SR-aGVHD) that is unresponsive to initial therapy with glucocorticosteroids has a 40% response rate to second line agents. Interleukin-6 has been implicated in the pathogenesis of aGVHD. Tociluzimab (TCZ) is an anti IL-6 monoclonal antibody and, to our knowledge, has not been previously reported for the treatment of aGVHD in children.

Methods, Intervention, & Analysis: We present a 3 year-old boy with a history of sickle cell disease who received a 7/8 matched unrelated donor AlloHCT. On day + 35, he was diagnosed with Grade IV intestinal aGVHD by both pathologic and clinical criteria. Symptoms included an ileus, stool output >1 liter/m2/day, persistent abdominal pain, and hematochezia. His abdominal pain was not controlled by escalating doses of either hydromorphone or fentanyl. Moderate relief was demonstrated with the combination of a ketamine drip and methadone. Initially the patient received methylprednisolone (2mg/kg/day), but was determined to be SR-aGVHD with worsening symptoms. He subsequently received multiple anti-GVHD agents at different time points, including mesenchymal stem cells, etanercept, basiliximab in combination with infliximab, pentostatin, and anti-thymocyte globulin. Despite these efforts, the patient exhibited no change in either symptomatology or histology. Approximately 2 months after the initial diagnosis of aGVHD, interleukin-6 levels were demonstrated to be 100 times the upper limit of normal. Salvage therapy with TCZ was initiated at a dose of 8mg/kg weekly for three weeks and then every other week for three subsequent doses. Within three weeks of the initiation of TCZ therapy, the patient showed an improvement in stool output and abdominal pain, subsequently narcotic were weaned off successfully. Eight weeks after discontinuation of TCZ, the patient developed a recurrence of abdominal pain and an intestinal biopsy was positive for grade I aGVHD. TCZ therapy was reinitiated on an every other week basis for four doses and a complete remission of aGVHD was achieved. At the time of writing this report, the patient no longer exhibits signs or symptoms of aGVHD and is in the process of being discharged after a 9-month hospitalization.

Findings & Interpretation: In the literature to date, there is just one case report of the use of TCZ in an adult with SR-aGVHD. An appropriate dose and schedule has not been established. Due to the severity of this child's disease and demonstrated lack of response to conventional therapies, we utilized TCZ as a salvage therapy and found it to be well tolerated and potentially life saving.

Discussion & Implications: Though our findings consist of this single patient, the dramatic improvement noted may demonstrate potential efficacy of TCZ in children with SR-aGVHD.

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Sub-Therapeutic Blood Tacrolimus Levels after Conversion from Continuous Intravenous (IV) Infusion to Per Oral (PO) are Associated with Higher Incidence of Acute Graft Versus Host Disease (AGVHD) in Children Following Allogeneic Hematopoietic Cell Transplant (AlloHCT)

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Topic Significance & Study Purpose/Background/Rationale: Limited data exists to determine the most appropriate conversion factor from IV to PO administration of tacrolimus in children receiving tacrolimus for aGVHD prophylaxis following AlloHCT. The incidence and impact of sub-therapeutic tacrolimus levels after conversion from IV to PO is also not well described.

Methods, Intervention, & Analysis: We retrospectively studied the association between length of time to achieve therapeutic tacrolimus levels (defined as >10ng/ml x 2 days) after conversion from IV to PO using the currently accepted factor of 4:1, as well as the incidence of grades I-IV aGVHD. aGVHD prophylaxis consisted of mycophenolate mofetil and tacrolimus. Tacrolimus was initiated at a dose of 0.03 mg/kg/day as a continuous IV infusion. The dose was adjusted to maintain trough levels within the range of 10-20 ng/mL. Once patients were able to tolerate oral medications they were transitioned to PO tacrolimus. Patients were kept in the hospital until they achieved therapeutic tacrolimus levels on PO. Patients were excluded if tacrolimus was initiated as IV and was never transitioned to PO or if they were started on PO and remained on PO for the duration of therapy.

Findings & Interpretation: Eighty-nine children (mean age, 8.3 yrs; range, 0.25-22: 60M/29F) undergoing AlloHCT for malignant (n= 52, 58.4%) and nonmalignant (n=37, 41.6%) disorders between March 2005 and April 2012 were identified. The overall incidence of Grade I-IV aGVHD was 48.3%. At the time of diagnosis of aGVHD, 20 patients (46.5%) were on IV tacrolimus, and 23 patients (53.5%) were on PO tacrolimus. Patients were transitioned to oral tacrolimus at a median of 23 days post-AlloHCT. After conversion to PO tacrolimus, the median and mean number of days to reach a therapeutic level was 7 and 10.2d (range 0-61), respectively. We compared the mean number of days to achieve therapeutic levels between those patients who developed aGVHD (n=43, 12.6 days) and those who with no aGVHD (n=46, 8.1 days), demonstrating that patients diagnosed with aGVHD took on average 4 days longer to achieve therapeutic levels on oral tacrolimus, which was statistically significant p=0.026 (t-test). Patients â‰¥ 12 yrs (n=31) when compared to patients <12 yrs (n=58) took a significantly longer time to achieve therapeutic levels (12.8 vs. 8.8 days t-test, p=0.05) after conversion from IV tacrolimus to PO. There was no significant association found between prior diagnosis of aGVHD and number of days required to obtain therapeutic tacrolimus levels.

Discussion & Implications: In conclusion, this data suggests that the longer a patient takes to achieve therapeutic tacrolimus levels after transitioning to PO, the greater their risk for developing aGVHD. Further analysis is ongoing to identify specific risk factors and patient populations who take longer than the median number of days to achieve therapeutic tacrolimus levels. This analysis may identify patients who